USE OF DIFFUSION RATES IN EVALUATING OINTMENT VEHICLES FOR ANTIBACTERIAL THERAPY*

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The successful use of antibacterial agents in ointment form depends on attaining a therapeutically effective local tissue concentration. The ointment must permit the drug to diffuse to the site of active bacterial growth. Bacterial cutaneous infections such as impetigo, ecthyma, deep ulcers, infectious eczematoid dermatitis, and secondarily infected dermatoses are all characterized by complete or partial disruption of the epidermis and exudation of extracellular and cellular fluid. The antibacterial drug must be released into this aqueous tissue fluid adequately and continuously if therapy is to be successful.

The diffusion and distribution of drug released from an ointment vehicle is dependent upon certain physiochemical factors such as the ionization constant of the drug, the degree of ionization in biological fluids (1) and the solubility of the ions and molecules in such fluids (2). These same factors play a role in the "penetration" of drugs into cellular and extracellular phases of tissue.

Clinical studies for the evaluation of the efficacy of various vehicles are time consuming, expensive, and require unusually large outpatient facilities. An objective in vitro method of determining the amount of an agent released from various vehicles, and the speed with which this occurs, should readily provide a rational basis for the selection of ointment vehicles. Although no in vitro method can guarantee that the identical results will be achieved in vivo, it does permit the elimination of obviously unsatisfactory bases and provides information regarding the relative values of the better vehicles as for example in the work done by Sulzberger, et al (3).

EXPERIMENTAL

The experiments were designed to simulate clinical conditions. The objective was to measure the amount of water-soluble drug released from various bases into a surrounding aqueous medium. Four types of bases readily available at any pharmacy were chosen for testing. These were: (1) grease bases—white petrolatum U.S.P., aquaphor, and hydrosorb;† (2) water-in-oil emulsion—unguentum aquae rosae U.S.P.; (3) oil-in-water emulsions—hydrophilic ointment U.S.P., a vanishing cream type base,‡ and an oil-in-water emulsion type base;§ and (4) water-soluble greaseless bases—carbowax 1500 and carbowax 4000.

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‡ Stearic acid 15 Gm., sodium carbonate 2 Gm., glycerin 15 cc., water 65 cc., and alcohol 3 cc.

§ Burroughs-Wellcome greaseless ointment base.

Sodium sulfadiazine was selected as the water-soluble chemotherapeutic agent for these tests because its solubility in the buffered saline solution used approximates that of other antibacterial agents such as sodium penicillin, calcium penicillin, streptomycin sulfate and bacitracin, and because its concentration can be determined with ease and accuracy. The ointments were compounded 5 per cent by weight of drug and 95 per cent of base.

Since the area of contact between ointment and surrounding fluid probably is a factor of importance, three types of experiments were conducted. In the first, the ointment was in a single small rounded mass; in the second, the ointment was spread to a thinness approximating that in topical treatment; and in the third, the ointment was in block form with only one surface in contact with the surrounding fluid. The area of this surface was constant for all ointment bases tested.

A weighed quantity of each of the test ointments was introduced through glass tubing into individual dialyzing bags of Visking seamless cellulose tubing having an inflated diameter of $\frac{27}{32}$ of an inch. In one experiment, the cellulose tubing measured 15 cm. in length and 3 cm. in width and the ointment was kept as a single globular mass about 1 cm. in diameter. In the second experiment, the cellulose tubing measured 30 cm. in length and the ointment was spread evenly over the entire interior of the bags to a thickness (0.1 cm.) comparable to that topically applied to a clinical lesion. In the third series, the ointments were packed into small petri dish covers (diameter 3.2 cm.) and carefully smoothed so that the area of exposure was constant.

Each petri dish cover was then placed into an individual beaker containing 200 cc. of solutions composed to resemble extracellular fluid; each dialyzing bag was put into a flask containing 100 cc. of the same solution. This freshly prepared solution contained per liter:

100 mM sodium chloride
27 mM sodium bicarbonate
15 mM sodium dihydrogen phosphate
5 mM potassium dihydrogen phosphate
2.5 mM magnesium sulfate
Final pH—7.4.

The solutions were then kept at 37°C. and covered to minimize evaporation. At intervals, aliquots were withdrawn and analyzed for sulfonamide by the Bratton-Marshall method, using a Klett-Summerson photoelectric colorimeter.

RESULTS

The amount of drug which left the ointment and moved into the solution is shown for various diffusion periods in Table 1 and Table 2. In Table 1, at the end of the 24-hour diffusion period, the almost negligible release of drug from grease and water-in-oil bases contrasts strikingly with the quantities released by oil-in-water and water-miscible bases. In the most extreme instance the difference was a thousandfold; and in every instance it was more than fifty fold. Table 2 shows that the same difference was obtained when the bases were in lump form. When the bases were spread out, the differences were tenfold, and in some in-

TABLE 1

Comparative amounts of sodium sulfadiazine diffusing into 200 cc. of buffered saline from various ointment bases when area of contact was constant at 30 sq. cm.

OINTMENT BASES	MGM. OF DRUG* AVAILABLE FOR DIFFUSION	DIFFUSION PERIODS			
		1 hr.	3 hr.	6 hr.	24 hr.
		mgm.	*mgm.*	*mgm.*	*mgm.*
White petrolatum	1630	0.12	0.16	0.40	0.40
Hydrosorb	1710	0.16	0.18	0.20	0.50
Cold cream	1700	0.60	0.60	0.60	1.00
Aquaphor	1640		0.16	0.36	2.86
Vanishing cream	1680	0.20	0.40	3.50	27.0
Carbowax 4000	2010	8.0	44.0	84.0	164.0
Greaseless base (B. W.)	1800	9.6	24.0	42.0	176.0
Hydrophilic ointment	1825	18.0	74.0	192.0	344.0
Carbowax 1500	2260		26.0	36.0	650.0

* Weight of ointment X 0.05.

TABLE 2

Comparative amounts of sodium sulfadiazine diffusing into 100 cc. of buffered saline from various ointment bases when (1) the base existed as a single mass in dialyzing bags and (2) the base was spread thinly over the interior of the dialyzing bags

OINTMENT BASES	MGM. OF DRUG* AVAILABLE FOR DIFFUSION	DIFFUSION PERIODS			PERCENTAGE OF DRUG DIFFUSED IN 24 HR.
		3 hr.	6 hr.	24 hr.	
		mgm.	*mgm.*	*mgm.*	
White petrolatum—single mass	230	0.25		0.6	0.002
—spread out	45	1.9	1.9	1.9	4.2
Aquaphor—single mass	50	0.4	0.4	0.4	0.8
—spread out	45	1.8	1.8	2.6	5.8
Vanishing cream—single mass	45	1.5	3.2	3.7	8.0
—spread out	55	3.5	4.0	8.0	15.0
Greaseless base—single mass	85	7.0	8.0	21.0	25.0
—spread out	85	18.0	22.0	44.0	52.0
Hydrophilic ointment—single mass	55	14.2	14.7	22.0	40.0
—spread out	55	20.0		23.0	41.0
Carbowax 4000—single mass	160	20.0	29.0	150.0	94.0
—spread out	40	26.0	39.2		98.0

* Weight of ointment X 0.05.

stances twentyfold. The results of duplicate sulfonamide determinations and duplicate experiments were consistent.

DISCUSSION

The experiments demonstrate a simple reproducible method of measuring rates of diffusion. While actual determinations of levels of drug in the exudates

of dermatoses would be preferable, the experimental procedure simulates clinical conditions closely enough to warrant consideration of the results by the practicing dermatologist. Other investigators have made observations on the suitability of bases for sulfonamide therapy (4, 5, 6, 7, 8, 9) and for penicillin therapy (10). All agree that water-soluble drugs are poorly released from grease bases. However, Macek, Gakenheimer, and Daugenbaugh (11) present a single observation of the complete release of penicillin from anhydrous petrolatum. In contrast the studies of Clymer and Ferlauto (10) show less than 1 per cent of the penicillin in a petrolatum base actually diffused into a surrounding aqueous medium.

Our own results show that ointment bases vary widely in the release of a water-soluble chemotherapeutic agent. Grease bases, water-absorbing bases, and water-in-oil emulsions release so little drug as to raise the question whether an effective level in an exudate is ever attained by their use.

Although sulfonamide "inhibitors" have been postulated to explain the frequent failure of locally applied sulfonamides, recent studies failed to demonstrate the existence of sulfonamide inhibitors in pus (12, 13). Since local therapy has usually been attempted with ointment bases which do not release drug or with insoluble powders, lack of an effective drug level may be the explanation for therapeutic failure.

This is a period of rapid development of antibiotic and chemotherapeutic agents which have an important place in clinical dermatology. Streptomycin, penicillin and bacitracin, all water-soluble medicaments, are undergoing clinical trial. It is apparent from these studies that if their value in topical application is to be properly appraised, the vehicle used must have the ability to deliver the drug to the desired place. Not only will there be a likelihood of therapeutic failure if an unsuitable vehicle is employed, but another serious disadvantage is the possibility that drug-resistant strains of bacteria may develop in an environment of sub-effective concentration.

No attempt is made here to consider the factor of stability of the drug in the various bases. Freshly compounded ointments that release the drug should be used rather than those ointments that provide prolonged stability of the drug but permit no diffusion.

CONCLUSIONS

Experiments were performed comparing the amounts and rates of diffusion of a water-soluble drug from various types of ointment vehicles into a buffered solution resembling extracellular fluid. The release of the drug from water-miscible bases and oil-in-water emulsions was 50 to 1000 times greater than its release from grease bases and water-in-oil emulsions.

The in vitro tests indicate the ability of water-miscible bases to release water-soluble antibacterial drugs into tissue fluids; in contrast, grease bases do not release such drugs into tissue fluids. For this reason, chemotherapeutic agents for local use should be incorporated into oil-in-water emulsions or in water-miscible bases.

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